

The Preparation, Condensation-Reactions and Physical Properties of 3-Phenyl-2, 4-Thiazolidione

DISSERTATION

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES OF THE
JOHNS HOPKINS UNIVERSITY IN CONFORMITY WITH
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

By

KLARE S. MARKLEY

EASTON, PA.
MACK PRINTING COMPANY
1933

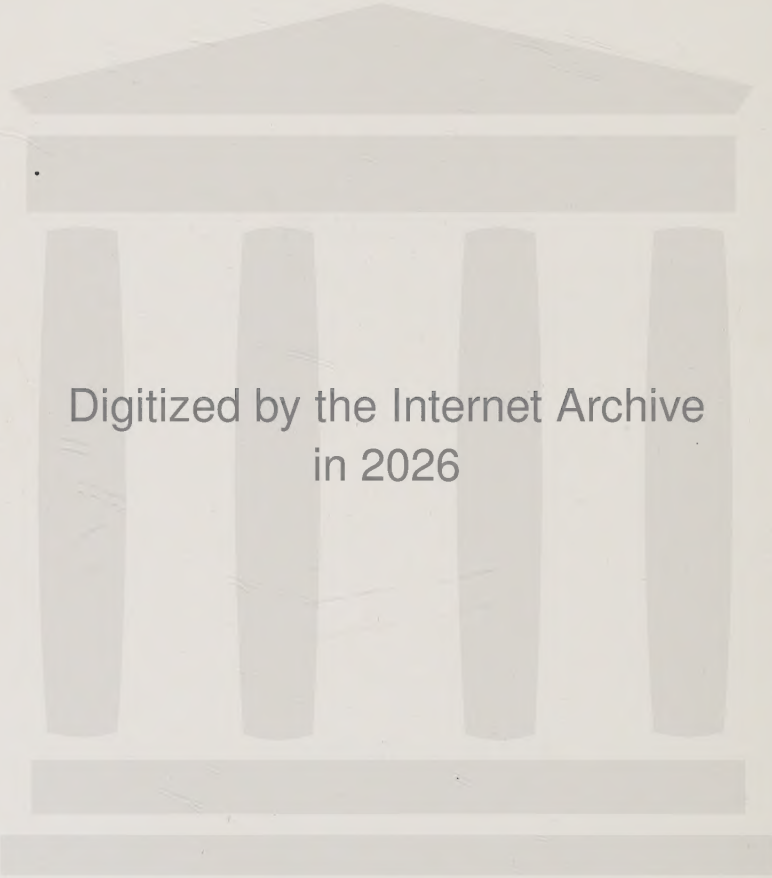
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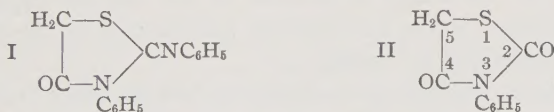
To Professors Frazer, Patrick, Rice and Cartledge of The Johns Hopkins University, whose lectures in related fields have ever been sources of inspiration, the writer also tenders his sincere appreciation.



THE REACTION BETWEEN THIOCARBANILIDE AND MONOCHLORO-ACETIC ACID IN ALCOHOL AND IN ACETIC ACID SOLUTION^{1,2}

Following the general directions of Lange³ for the preparation of diphenylisothiohydantoin from thiocarbanilide and monochloro-acetic acid, in order to study its condensation with aldehydes, Hann and Markley⁴ and later Kingsbury and Markley⁵ observed that the reaction conditions markedly affected not only the yield but also the compound which was formed. No explanation of these observations could be obtained from the papers of Lange, Andreasch,⁶ Liebermann and Lange,⁷ and Liebermann,⁸ who previously prepared diphenylisothiohydantoin for the purpose of studying its constitution, since these authors failed to mention either the yields obtained or the effect of variations in the experimental conditions on the reaction. A number of experiments were therefore undertaken to determine what influence the concentration of reactants, time of reflux, solvent and catalyst had on the course of the reaction.

Results and Discussions.—As a result of this investigation it has been determined that, irrespective of solvent, the primary reaction between thiocarbanilide and monochloro-acetic acid is the formation of diphenylisothiohydantoin (I). From the results recorded in Table I it is evident



that with alcohol as solvent the best yields are obtained with a short period of reflux, a small ratio of solvent to reactants, a slight excess of monochloro-acetic acid and the addition of sufficient anhydrous sodium acetate to remove the hydrochloric acid from the reaction as rapidly as it is formed. A high yield of diphenylisothiohydantoin may likewise

¹ Presented in abstract before the Organic Division at the Columbus meeting of the American Chemical Society, April, 1929.

² Markley and Reid, *J. Am. Chem. Soc.*, **52**, 2137 (1930).

³ Lange, *Ber.*, **12**, 595 (1879).

⁴ Hann and Markley, *J. Washington Acad. Sci.*, **16**, 169 (1926).

⁵ Kingsbury and Markley, *ibid.*, **18**, 558 (1928).

⁶ Andreasch, *Ber.*, **12**, 1385 (1879).

⁷ Liebermann and Lange, *ibid.*, **12**, 1588 (1879).

⁸ Liebermann, *Ann.*, **207**, 121 (1881).

be obtained with glacial acetic acid as solvent provided precautions are taken to remove the hydrogen chloride formed in the primary reaction.

TABLE I

EFFECT OF REACTION CONDITIONS UPON THE YIELD OF DIPHENYLISOTHIOHYDANTOIN

No.	(C ₆ H ₅ -NH) ₂ CS,		CH ₂ Cl-COOH,		Solvent used		Other reagents used		Time of reflux, hours	Crude diphenylisothiohydantoin		
	g.	g.	Kind	cc.	Kind	Amount	Kind	Amount		g. ^a	%	% N ^b
1	25	10.5	95% alc.	400		...		...	4.5	10.8	36.8	10.38
2	25	12.0	95% alc.	400		...		...	4.5	11.6	39.5	10.42
3	50	25.0	95% alc.	400		...		...	2.5	25.0	42.5	10.26
4	25	12.0	95% alc.	300		...		...	2.5	13.0	44.2	10.74
5	25	12.0	95% alc.	300		...		...	2.0	13.0	44.2	10.28
6	100	45.0	95% alc.	400		...		...	1.25	54.0	45.9	10.38
7	100	50.0	95% alc.	500		...		...	1.25	58.0	49.3	...
8	25	12.0	100% alc.	200		...		...	2.5	13.0	44.2	10.27
9	50	25.0	100% alc.	300	CH ₃ COONa	10 g.		...	3.5	45.0 ^c	76.6	...
10	50	25.0	CH ₃ COOH	60		...		...	5.5	..	..	..
11	25	12.0	CH ₃ COOH	75	CH ₃ COONa	10 g.		...	2.0	24.0 ^c	81.7	10.38
12	25	12.0	95% alc.	500	HCl	10 cc.		...	5.5	..	..	...

^a The actual yields are somewhat higher due to the slight solubility of the compound in 95% alcohol. ^b Theoretical nitrogen: 10.45%. ^c Reaction mixture treated with water to separate the CH₃COONa.

When these precautions are not observed a mixture of diphenylisothiohydantoin and 3-phenyl-2,4-thiazolidione⁹ (II) is formed in alcohol solution, whereas with glacial acetic acid (in proper proportion)¹⁰ as the solvent and provided the time of reflux is sufficiently prolonged (five hours or more), practically quantitative yields of the latter compound are obtained, as indicated in Table II. It is apparent that the cyclic diketone results from the secondary hydrolysis of the diphenylisothiohydantoin under the influence of the hydrochloric acid formed in the primary reaction, as was suggested by Lange.

The hydrolysis of diphenylisothiohydantoin to form 3-phenyl-2,4-thiazolidione, however, is not the only factor which lowers the yield of diphenylisothiohydantoin as prepared in alcoholic solution, since the mother liquors from these preparations were found to contain, in addition to 3-phenyl-2,4-thiazolidione, urea, phenyl mustard oil and phenylthiourethan. The addition of hydrochloric acid to the original reaction mixture (Expt.

⁹ Liebermann and Völtzkow, *Ber.*, **13**, 276 (1880), obtained the same compound by heating phenylthiourethan, monochloro-acetic acid and absolute alcohol under pressure; P. Meyer, *Ber.*, **14**, 1659 (1881), by the hydrolysis of *o*-phenylthiohydantoic acid and *o*-phenylthiohydantoin; Evers, *ibid.*, **21**, 962 (1888), by the reaction of ethyl-, propyl- and allylphenylthiourethan and monochloro-acetic acid; Wheeler and Barnes, *Am. Chem. J.*, **24**, 60 (1900), by melting together phenylthiourethan and monochloro-acetic acid.

¹⁰ If the volume of glacial acetic acid is too large, diphenylisothiohydantoin is not completely converted into the cyclic diketone; if too small, partial decomposition ensues with the formation of phenyl mustard oil.

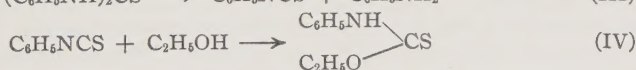
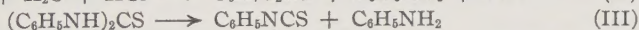
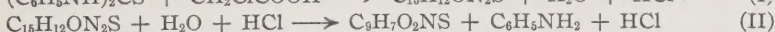
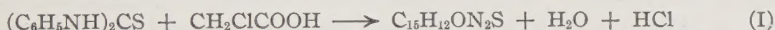
TABLE II

EFFECT OF REACTION CONDITIONS UPON THE YIELD OF 3-PHENYL-2,4-THIAZOLIDIONE

No.	(C ₆ H ₅ -NH) ₂ CS, g.	CH ₂ Cl- COOH, g.	CH ₃ - COOH, cc.	Time of reflux, hours	Yield of crude diketone g.	%	Solvent used for final crystalliza- tion	Purified compound, % N ^a
1	50	25	75	2.5	43 ^b	..		..
2	25	12	25	2.0	16 ^c	..		..
3	50	25	100	4.25	27 ^d	..		..
4	25	12	40	4.0	18 ^e	..		..
5	25	12	25	4.25	14	66.2	Not recryst.	7.27
6	50	25	65	4.5	36	85.1	CH ₃ COOH	7.35
7	25	12	25	4.0	18.3	86.5	CH ₃ COOH	7.23
8A	50	25	60	5.5	40	94.3	95% alc.	7.27 ^f
8B	50	25	60	5.5	39	92.2	CH ₃ COOH	
9	25	12	30 ^g	3.0	14	66.2	Not recryst.	7.28

^a Theoretical nitrogen, 7.25%. ^b 17.0 g. of diphenylisothiohydantoin separated from crude product. ^c 4.5 g. of diphenylisothiohydantoin isolated from crude product. ^d Analysis of crude compound gave 8.53% N; impurity found to be diphenylisothiohydantoin. ^e Nitrogen of crude product, 8.83%. Diphenylisothiohydantoin isolated from mixture. ^f After drying at 133°. ^g 10 cc. of concd. HCl added to reflux mixture; considerable phenyl mustard oil formed.

12, Table I) led to the formation of but small amounts of diphenylisothiohydantoin and 3-phenyl-2,4-thiazolidione and considerable quantities of phenyl mustard oil and phenylthiourethan, whereas the addition of hydrochloric acid to an alcoholic solution of diphenylisothiohydantoin led to its quantitative transformation into 3-phenyl-2,4-thiazolidione. Summarizing these results, the following reactions may be assumed to occur during the reaction of thiocarbanilide with monochloro-acetic acid in alcohol solution.



Experimental

Diphenylisothiohydantoin.—The general method used in preparing the diphenylisothiohydantoin was briefly as follows: 25 to 100 g. of thiocarbanilide and slightly more than the corresponding molar quantity of CH₂ClCOOH were dissolved in 300 to 500 cc. of alcohol and heated under a reflux condenser for one and one-fourth to five hours. As long as the solid phase of the compound was absent, no crystals separated although the solution was enormously supersaturated with respect to diphenylisothiohydantoin. At the expiration of the time of refluxing, the hot solution was filtered with the aid of a hot water funnel. The diphenylisothiohydantoin separated from the hot filtrate in beautifully iridescent, very thin plates. When the volume of alcohol was sufficiently large the compound was found to separate in a very pure form as was shown by nitrogen analysis and melting point. When the compound was recrystallized, 3 to 5 times the volume of boiling alcohol was necessary to redissolve it as compared with the original

volume of solvent from which it was obtained. Upon pouring the hot alcoholic solution into cold water, pure diphenylisothiohydantoin separated as a white microcrystalline powder and not as an oil as was reported by Lange. It did, however, separate as a red oil from the crude reaction mixture when the latter was treated with water in a similar manner. A solubility determination of diphenylisothiohydantoin in 95% alcohol at 27° gave a value of 0.35 g. per 100 g. of solvent, or 0.28 g. per 100 cc. The optical properties of diphenylisothiohydantoin as determined by Mr. G. L. Keenan of the Bureau of Chemistry and Soils were as follows. Recrystallized from 95% alcohol the compound consisted of thin, colorless, micaceous plates. The indices of refraction were found to be n_α 1.654, n_β 1.690, both ± 0.003 , $n_\gamma > 1.734$. In convergent polarized light, crossed nicols, biaxial interference figures were observed occasionally, particularly in plates perpendicular to an optic axis.

3-Phenyl-2,4-thiazolidione.—Since the condensation of diphenylisothiohydantoin with aromatic aldehydes is readily effected in glacial acetic acid, it was thought that this acid would prove to be an ideal solvent for its preparation. Nitrogen analysis, melting point and microscopic examination of the resulting product showed, however, that the compound formed was 3-phenyl-2,4-thiazolidione and not the expected diphenylisothiohydantoin. Almost quantitative yields were obtained when the following conditions were observed: 50 g. of $(C_6H_5NH)_2CS$, 25 g. of $CH_2ClCOOH$ and 60 cc. of glacial acetic acid were shaken together in a 300-cc. flask to form a paste. Partial solution occurred, accompanied by considerable cooling. The flask was connected with a reflux condenser and gentle heat applied to effect complete solution, after which vigorous boiling was maintained for five hours or more. On cooling, the contents of the flask solidified to a mass of star-shaped clusters of yellow needles quite unlike diphenylisothiohydantoin. Following the addition of water the mass was disintegrated by shaking, and the product washed first by decantation and then on a Büchner funnel. On recrystallization from alcohol it separated in the form of bushy rosetts of long thin yellow needles.

Mother Liquors of Diphenylisothiohydantoin.—When the mother liquors from the alcohol series of preparations, which always possessed a typical phenyl mustard oil odor, were evaporated either by the aid of heat or spontaneously, crystallization continued with the separation of a compound which appeared to the casual view to be diphenylisothiohydantoin. When evaporation was continued to dryness it was observed that two different layers formed; an upper one which appeared like diphenylisothiohydantoin and a lower one composed of a dark red, oily material shot through with fine needle-like crystals. When heated to 100° or to an even lower temperature the whole mass melted to a clear red oil which solidified again on cooling. Examination of the mother liquors from Preps. 3, 5, 7 and 8 (Table I) led to the isolation and identification of the following compounds: phenyl mustard oil, phenylthiourethan, diphenylisothiohydantoin, 3-phenyl-2,4-thiazolidione and diphenylthiourea. Although quantitative separations were impracticable, it appeared that phenyl mustard oil and phenylthiourethan comprised the bulk of the products contained in the mother liquors.

In addition to the experiments recorded in Tables I and II, two additional preparations were made by refluxing for two hours 25 g. of diphenylthiourea and 12 g. of $CH_2ClCOOH$ dissolved in 300 and 250 cc. of 95% alcohol, respectively. After separating the crystallized diphenylisothiohydantoin in the usual manner, the mother liquors and washings were evaporated until but 25 to 35 cc. of a red oil remained, which on cooling solidified to a light yellow crystalline mass. To the first residue there was added 5 g. of $CH_2ClCOOH$, 5 cc. of concd. hydrochloric acid and 60 cc. of acetic acid, and to the second 25 cc. of acetic acid only. Both mixtures were then refluxed for four hours. After cooling the reaction mixtures were poured into large volumes of cold water and allowed to stand for twenty-four hours to separate the crystalline material from the oil. The

crude product which separated was then collected on a Büchner funnel, washed with water, dried and weighed. In the first case diphenylisothiohydantoin and 3-phenyl-2,4-thiazolidione equivalent to 49.4 and 17.5% and in the second case 42.5 and 26%, respectively, of the original thiocarbanilide were recovered.

Secondary Formation of 3-Phenyl-2,4-thiazolidione.—Since hydrochloric acid separated in molar proportions in the course of the reaction, its effect on diphenylisothiohydantoin and the original reactants was studied in this concentration. Two samples of 10 g. each of pure diphenylisothiohydantoin were dissolved in 60 cc. of glacial acetic acid and 1.35 g. of hydrochloric acid added in the form of its concentrated aqueous solution. To the second sample was added 5 g. of anhydrous sodium acetate. Both samples were boiled under a reflux condenser for four hours. Upon cooling, the reaction mixtures were poured into large volumes of cold water, the precipitates collected on Büchner funnels and washed to remove the acetic acid, hydrochloric acid and sodium acetate. After drying at 105°, the product from the first reaction, amounting to 7.0 g. (calcd. 7.2 g.), was identified by microscopic examination and nitrogen analysis as 3-phenyl-2,4-thiazolidione. The diphenylisothiohydantoin was quantitatively recovered in the second case.

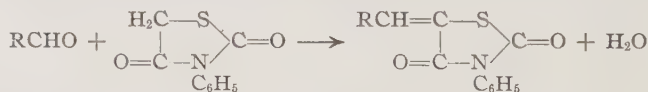
Summary

The reaction between thiocarbanilide and monochloro-acetic acid has been studied in alcohol and in acetic acid under different experimental conditions and the probable mechanism of the reaction established. With anhydrous solvent containing sufficient anhydrous sodium acetate to remove both the water and hydrogen ions from the sphere of action, the maximum yield of diphenylisothiohydantoin is obtained. With acetic acid as solvent and a period of refluxing exceeding five hours, almost quantitative yields of 3-phenyl-2,4-thiazolidione are obtained.

CONDENSATION OF 3-PHENYL-2,4-THIAZOLIDIONE WITH AROMATIC ALDEHYDES^{1,2}

It has long been known that heterocyclic compounds containing the linkage $\text{—SCH}_2\text{CO—}$ undergo condensation with aromatic aldehydes³ and with substances like phthalic anhydride and nitrosodimethylaniline,⁴ isatin,⁵ alloxan⁶ and phenanthraquinone.⁷ The reaction conditions and the ease with which condensation occurs depend on the substituents in the heterocyclic ring and upon the nature of the oxygen-containing compound with which it reacts. Among the substances containing the above-mentioned linkage is 3-phenyl-2,4-thiazolidione, which is particularly reactive with aromatic aldehydes.

Ruhemann⁸ condensed benzaldehyde, salicylaldehyde, cinnamic aldehyde and piperonal with it, employing alcohol as the solvent and piperidine as catalyst. Andreasch⁹ condensed the first two of these aldehydes employing glacial acetic acid as solvent and anhydrous sodium acetate as a dehydrating agent. Since condensation occurs as a result of the splitting out of water between the methylene hydrogen of the parent substance and oxygen of the aldehyde in accordance with the equation



it is obvious that the latter method is preferable.

In view of the fact that the reaction between 3-phenyl-2,4-thiazolidione and aromatic aldehydes takes place readily and smoothly with the formation of easily isolable, stable crystalline products, a number of condensations were carried out to determine the applicability of the method for the characterization of individual members of this class of compounds.

¹ Presented in abstract before the Organic Division at the Columbus meeting, April, 1929.

² Markley and Reid, *J. Am. Chem. Soc.*, **52**, 2981 (1930).

³ Nencki, *Ber.*, **17**, 2277 (1884); Andreasch, *Monatsh.*, **8**, 407 (1887); Hann and Markley, *J. Wash. Acad. Sci.*, **16**, 169 (1926); Kingsbury and Markley, *ibid.*, **18**, 558 (1928).

⁴ Kučera, *Monatsh.*, **35**, 137 (1914).

⁵ Andreasch, *ibid.*, **38**, 135 (1917).

⁶ Butscher, *Monatsh.*, **32**, 9 (1911).

⁷ Raymond M. Hann, Master's thesis, George Washington University, 1926.

⁸ Ruhemann, *J. Chem. Soc.*, **95**, 117 (1909).

⁹ Andreasch, *Monatsh.*, **38**, 125 and 127 (1917).

TABLE I

3-PHENYL-2,4-THIAZOLIDIONE CONDENSATION WITH AROMATIC ALDEHYDES

Prepn.	Aldehyde Name	g.	C ₆ H ₅ O ₂ NS, g.	CH ₃ COOH, cc.	Time of reflux, hours	Yield of condensation product	
						g.	%
1	<i>p</i> -Tolualdehyde	1.5	2.0	25	5.0	2.2	72
2	<i>p</i> -Hydroxybenzaldehyde	3.4	5.0	35	2.0	5.0	65
3	<i>o</i> -Chlorobenzaldehyde	3.7	5.0	35	2.25	5.0	61
4	Vanillin	4.0	5.0	35	2.25	5.5	65
5	Veratraldehyde	2.35	2.5	35	2.75	2.0	45
6	Piperonal	3.0	3.0	35	2.50	3.0	59
7	Furfural	3.0	4.0	60	2.0	...	^a
8	Anisaldehyde	3.0	4.0	35	2.25	4.0	83
9	<i>o</i> -Methoxybenzaldehyde	1.5	2.0	25	2.50	2.5	78
10	Benzaldehyde	2.5	4.0	30	2.0	4.0	69
11	Salicylaldehyde	2.7	5.0	30	2.25	3.5	46
12	<i>m</i> -Nitrobenzaldehyde	4.0	5.0	40	2.50	3.0	36
13	Cinnamic aldehyde	3.0	4.0	40	3.0	4.5	71

^a Preparation not weighed; another preparation gave 71% yield.

Results and Discussion.—Sixteen aromatic aldehydes were condensed with 3-phenyl-2,4-thiazolidione using glacial acetic acid as solvent and anhydrous sodium acetate as the dehydrating agent. Reaction occurred with the formation of well crystallized, stable products in good yield with all except resorcyaldehyde, hydrocinnamaldehyde and 2,4,6-trinitrobenzaldehyde, with which the reaction occurred to some extent but pure compounds were not isolated from the reaction mixtures. Sharp melting points were observed with most of the products although some of them partially sublimed before melting, a behavior which is also characteristic of the parent substance.

The data concerning the reaction conditions, the yield, melting point and nitrogen content of the products are recorded in Tables I and II. Ruhemann reported the melting points of the benzylidene and salicylidene compounds at 208–209° and 238–239°, respectively, after recrystallization from alcohol; Andreasch gives 239 and 140°, respectively, whereas our compounds after recrystallization from glacial acetic acid melted at 210–211° and 235–236°, respectively.

Experimental

The parent substance, 3-phenyl-2,4-thiazolidione, was prepared by refluxing thiocarbanilide and monochloro-acetic acid for five hours in glacial acetic acid solution in accordance with the procedure described in a previous part of this paper.¹⁰

The aldehyde condensations were carried out by dissolving 2 to 5 g. of 3-phenyl-2,4-thiazolidione together with slightly more than the theoretical

¹⁰ Markley and Reid, *J. Am. Chem. Soc.*, **52**, 2137 (1930).

TABLE II

ANALYSES AND PHYSICAL CHARACTERISTICS OF THE ALDEHYDE CONDENSATION PRODUCTS

Prepn.	Condensation product	Physical appearance
1	5- <i>p</i> -Tolual-3-phenyl-2,4-thiazolidione	Pale yellow needles
2	5- <i>p</i> -Hydroxybenzal-3-phenyl-2,4-thiazolidione	Short, thick lemon-yellow needles
3	5- <i>o</i> -Chlorobenzal-3-phenyl-2,4-thiazolidione	White, filamentous crystals
4	5-Vanillal-3-phenyl-2,4-thiazolidione	Bright yellow fragmented plates
5	5-Veratral-3-phenyl-2,4-thiazolidione	Long, bright yellow needles
6	5-Piperonal-3-phenyl-2,4-thiazolidione	Slender, bright yellow needles
7	5-Furfural-3-phenyl-2,4-thiazolidione	White, filamentous crystals
8	5-Anisal-3-phenyl-2,4-thiazolidione	Pale yellow, filamentous crystals
9	5- <i>o</i> -Methoxybenzal-3-phenyl-2,4-thiazolidione	Pale yellow microcrystalline powder
10	5-Benzal-3-phenyl-2,4-thiazolidione	White, microcrystalline powder
11	5-Salicylal-3-phenyl-2,4-thiazolidione	Brownish, yellow needles
12	5- <i>m</i> -Nitrobenzal-3-phenyl-2,4-thiazolidione	Pale yellow, microcrystalline powder
13	5-Cinnamal-3-phenyl-2,4-thiazolidione	Brilliant yellow needles

Formula	Weight, g.	Nitrogen-K. G. A. method			M. p., °C.
		N/14 H ₂ SO ₄ consumed, cc.	Nitrogen, % Found	Calcd.	
C ₁₇ H ₁₃ O ₂ NS	0.3205	15.36	4.79	4.75	192
C ₁₆ H ₁₁ O ₃ NS	.2575	12.29	4.77	4.71	257.5
C ₁₆ H ₁₀ O ₂ CINS	.2897	13.02	4.49	4.44	169-170
C ₁₇ H ₁₃ O ₄ NS	.2537	11.09	4.37	4.28	234-235
C ₁₈ H ₁₅ O ₄ NS	.2843	11.39	4.01	4.10	208-209
C ₁₇ H ₁₁ O ₄ NS	.3407	14.52	4.26	4.31	207-208
C ₁₄ H ₉ O ₃ NS	.2942	15.17	5.16	5.17	218-219
C ₁₇ H ₁₃ O ₃ NS	.2975	13.22	4.44	4.50	199-200
C ₁₇ H ₁₃ O ₃ NS	.2015	8.61	4.27	4.50	138-139
C ₁₆ H ₁₁ O ₂ NS	.2805	13.59	4.84	4.98	210-211
C ₁₆ H ₁₁ O ₃ NS	.2227	10.58	4.75	4.71	235-236
C ₁₆ H ₁₀ O ₄ N ₂ S	.2669	22.70	8.51	8.59	188
C ₁₈ H ₁₃ O ₂ NS	.2535	11.53	4.55	4.56	212-213

amount of the appropriate aldehyde, in 25 to 40 cc. of glacial acetic acid containing 5 g. of anhydrous sodium acetate and heating under a reflux condenser for one and one-half to five hours. The reaction product upon cooling almost always solidified in a characteristic crystalline mass. After the addition of water, the mass was disintegrated by shaking, the fine crystalline meal thrown on a Büchner funnel, thoroughly washed with water and usually with small amounts of glacial acetic acid, 50% alcohol and again with water to insure complete removal of the sodium acetate and excess aldehyde. After drying and determining the crude yields, the compounds were recrystallized from glacial acetic acid.

The nitrogen determinations were carried out in accordance with the

usual Kjeldahl-Gunning-Arnold procedure except that boric acid¹¹ was substituted for standard alkali for the absorption of the evolved ammonia, which was then directly titrated with *N*/14 sulfuric acid.

An electrically heated melting point apparatus and Wheeler completely immersed thermometers, standardized by the U. S. Bureau of Standards, were used in determining the melting points of the compounds. They were usually immersed at a temperature approximately 10° below the roughly determined melting point and the temperature was allowed to rise slowly to the observed melting point.

Summary

Thirteen aromatic aldehydes were condensed with 3-phenyl-2,4-thiazolidione and the products isolated and described. The physical appearance, melting point and nitrogen analysis of the resulting product are sufficiently distinctive to warrant the use of the method for the characterization of aromatic aldehydes.

¹¹ Markley and Hann, *J. Assn. Off. Agri. Chem.*, **8**, 455 (1925).

POLYMORPHISM IN THE SUBSTITUTED THIAZOLE, 3-PHENYL-2,4-THIAZOLIDIONE¹

In the course of a study of the reaction between monochloroacetic acid and thiocarbanilide Markley and Reid² repeatedly prepared quantities of 3-phenyl-2,4-thiazolidione and recrystallized each preparation from hot glacial acetic acid. Thus obtained, the compound melted at 143–144°, as determined by the capillary tube method, in which a totally immersed thermometer and electrically heated melting apparatus³ was used. Repeated crystallization from glacial acetic acid failed to effect a change in the melting point of the compound but after recrystallization from hot water it melted at 147–148°. Subsequent recrystallization from acetic acid caused a reversion of the melting point to 143–144°.

Lange,⁴ the first to prepare 3-phenyl-2,4-thiazolidione, reported its melting point as 148°. Liebermann and Völtzkow⁵ and later Meyer⁶ reported the melting point of their preparations as 148° and Wheeler and Barnes⁷ gave it as 147–148°. Evers,⁸ however, reported 143° as the melting point of each of his three different preparations of 3-phenyl-2,4-thiazolidione. All of these authors mention several different solvents from which the compound can be crystallized but they do not state which solvent they used in crystallizing the preparation prior to determining the melting point.

Analyses of the preparations reported by Markley and Reid as well as additional ones made in the course of the present investigation indicated that the compound was pure and contained no solvent of crystallization. This was true also of a number of samples crystallized from 95% alcohol and melting at 147–148°, and of one sample crystallized from 50% alcohol and melting at 143–144°. When sublimed, the compound was found to melt at 143–144° or 147–148° and in some cases at intermediate temperatures, depending upon the conditions of sublimation.

It seemed probable that the differences in the melting temperatures of the samples were attributable to the fact that 3-phenyl-2,4-thiazolidione occurred in at least two different crystalline forms. From such partial optical data as could be obtained initially it was impossible to say definitely

(1) Gibson and Markley, *J. Am. Chem. Soc.*, **55**, 2399 (1933).

(2) Markley and Reid, *J. Am. Chem. Soc.*, **52**, 2137 (1930).

(3) Sando, *Ind. Eng. Chem., Anal. Ed.*, **3**, 65 (1931).

(4) Lange, *Ber.*, **12**, 595 (1879).

(5) Liebermann and Völtzkow, *ibid.*, **13**, 276 (1880); *Ann.*, **207**, 137 (1881).

(6) Meyer, *Ber.*, **14**, 1659 (1881).

(7) Wheeler and Barnes, *Am. Chem. J.*, **24**, 60 (1900).

(8) Evers, *Ber.*, **21**, 962–977 (1888).

that the compound existed in different crystalline forms; later Dr. H. E. Merwin found slight but significant differences in the optical properties of the various samples which will be given in detail at the end of this paper.

In order to demonstrate the polymorphism of 3-phenyl-2,4-thiazolidione we resorted to thermal analysis—by heating and cooling curves—to dilatometer experiments, and to x-ray diffraction photographs which were kindly taken for us by Dr. Sterling B. Hendricks of the Fixed Nitrogen and Fertilizer Division of the United States Department of Agriculture. The results showed clearly that this compound does exist in two polymorphic modifications, the form which melts at 143–144° (usually obtained from glacial acetic acid solution) being stable at room temperature, whereas the form melting at 147–148° (obtained from aqueous solution) is stable at temperatures above *ca.* 100°.

Experimental

Thermal Analysis.—With the apparatus shown diagrammatically in Fig. 1 thermal effects during the heating and cooling of the various samples were observed. The sample of 3-phenyl-2,4-thiazolidione was contained in the double jacketed vessel A and its temperature was observed by the thermocouple B—a single junction of No. 30 constantan and No. 36 copper wires. The thermocouple was enclosed in a thin-walled glass tube just large enough to admit the wires. The melting tube A was immersed in oil contained in a Dewar flask. The oil was heated and stirred by the assembly S. A thermocouple D, immersed in the oil-bath, was connected in series with B so that the temperature difference between the junctions of B and D could be measured directly; this gave the “differential temperature,” the criterion of latent-heat changes in the sample. In an experiment the current was adjusted so that the bath heated uniformly at a constant rate (0.5–1.5° per min.); readings of the temperature of the sample, the e. m. f. of the thermocouple B, and of the “differential temperature” were taken at half- or quarter-minute intervals. The “differential temperature” was plotted as ordinate against the temperature of the sample as abscissa, curves similar to those in Figs. 2 and 3 being obtained. As long as no reaction took place in the melting tube the curve was roughly parallel to the temperature axis, but heat absorption or emission accompanying a change of phase was manifested by a sharp increase or decrease in the “differential temperature.” In all our experiments a positive “differential temperature” indicated that the sample was cooler than the bath—the normal state of affairs on heating.

Calibration of Thermocouples.—The thermocouples were standardized by comparison in a well-stirred bath with a special single junction element which had been calibrated at the U. S. Bureau of Standards. It was found that in the region between 0 and 200° the table of temperature as a function of e. m. f. given for copper-constantan elements in the “International Critical Tables”⁹ could be used without any

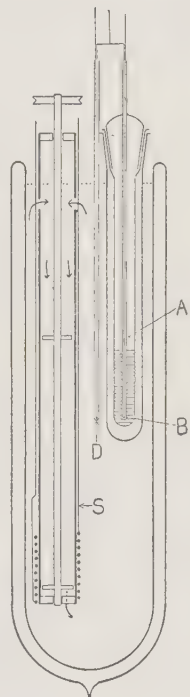


Fig. 1.—Apparatus for detection of phase changes by observation of thermal effects.

(9) "International Critical Tables," Vol. 1, p. 58 (1926).

deviation curve for computing the temperature in degrees Centigrade from the observed reading in microvolts.

Heating Curves.—Curve I in Fig. 2 is the significant portion of the heating curve of a sample of 3-phenyl-2,4-thiazolidione crystallized from aqueous solution and melting in a capillary tube at 148° . It will be seen that there is only one break, around 6500 microvolts (146°), due in fact to the absorption of heat by the sample on melting. On the other hand, curve II, obtained with a sample recrystallized from glacial acetic acid (m. p. $143\text{--}144^{\circ}$), shows that a reaction takes place when the temperature is about 139° . Moreover, it was observed that the state of aggregation of the compound did not change during this absorption of heat. On being heated further the compound

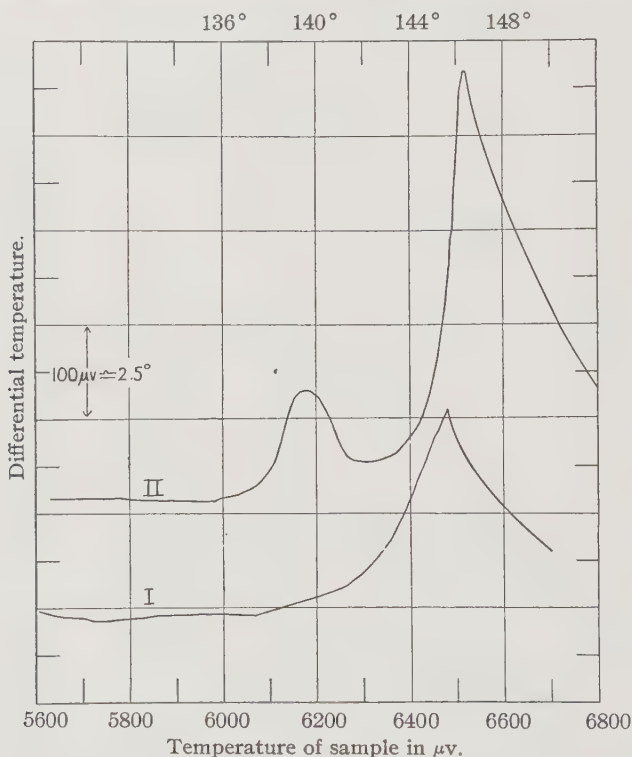


Fig. 2.—Heating curves for the two forms of 3-phenyl-2,4-thiazolidione. Curve I represents compound crystallized from water and Curve II the same compound crystallized from glacial acetic acid. The ordinate represents the difference between the temperature of the bath and that of the sample and the abscissa gives the temperature of the sample in microvolts at the bottom of the diagram and degrees Centigrade at the top.

melted at 146° as did the sample crystallized from water. Curve II, which is one of many similar curves obtained with the lower melting samples, showed definitely that at $139\text{--}141^{\circ}$ the samples of 3-phenyl-2,4-thiazolidione, melting at $143\text{--}144^{\circ}$ in a capillary tube, which we shall now call Form II, undergo a rapid solid-solid transformation to the higher temperature modification, Form I. It may be remarked parenthetically

that although Form II always appeared to melt at 143–144° in a capillary tube, it never melted at this temperature in the heating curve apparatus. The curves in Fig. 3 were obtained as follows. A sample recrystallized from glacial acetic acid was heated in the melting tube. After the usual heat effect around 139° (curve I) had taken place, the sample was withdrawn from the bath and allowed to cool in the air. The sample was replaced in the bath, kept at room temperature overnight, and the

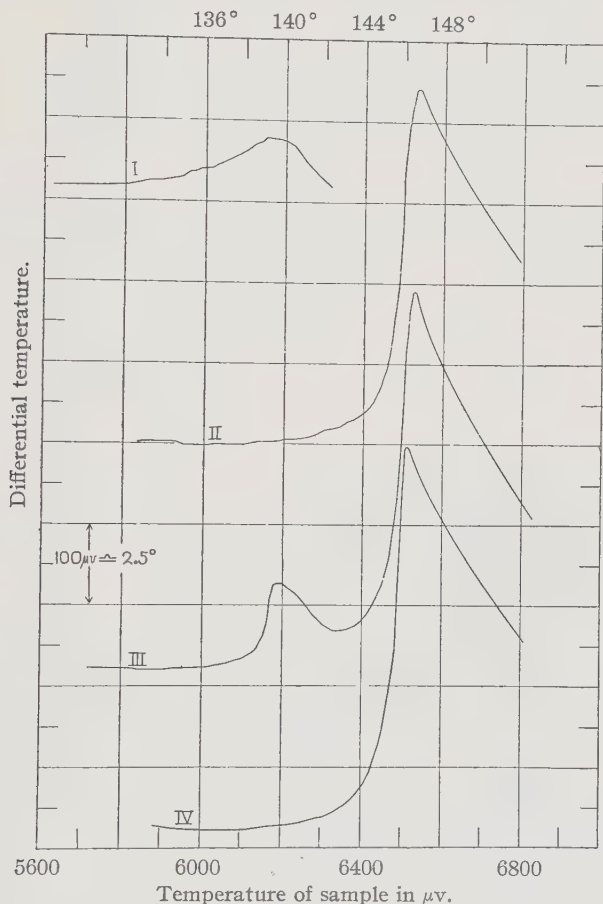


Fig. 3.—Heating curves of 3-phenyl-2,4-thiazolidione treated in different ways.

next day another heating curve, curve II, was obtained. This time no heat effect was observed until melting began; the specimen behaved like the usual product from aqueous solution. Curves III and IV in Fig. 3 were obtained from observations on the same sample of 3-phenyl-2,4-thiazolidione that was used in the experiment which gave curve II, Fig. 2. This sample was melted, then chilled rapidly, and it was observed that Form II crystallized from the melt. Its behavior on reheating is illustrated by curve III which shows the two breaks at 139 and 146°, respectively. The

melted material was then allowed to cool slowly and was seeded with Form I. On crystallization the temperature rose to 145° after which the whole was cooled slowly in the bath to room temperature. The heating curve of the sample so treated is curve IV in Fig. 3.

From the thermal analyses, therefore, it may be concluded first, that two modifications of 3-phenyl-2,4-thiazolidione exist, Form I which melts at 146° (in a capillary tube at $147\text{--}148^{\circ}$)¹⁰ and Form II which inverts to Form I at about 139° when heated; second, that, as the results illustrated in Fig. 3 show, this inversion is not readily reversible; Form I does not change back to Form II when the temperature is lowered but may remain unchanged for a long time at room temperature; and third, that by suitable treatment either solid modification may be obtained from the same liquid phase. It should be remarked that in one case a sample, crystallized from water under special conditions, gave a heating curve which exhibited two heat effects.

Dilatometer Experiments.—A sample of 3-phenyl-2,4-thiazolidione was enclosed in the liquid state over mercury in a glass dilatometer. In this way air bubbles were excluded. On account of the impossibility of ensuring that only one form of the solid was present no quantitative measurements could be made. It was found, however, that an anomalous expansion of the solid occurred rapidly in the neighborhood of 136° . This corresponded to the first break in the heating curve of Form II. In addition it was found that this anomalous expansion could be observed to

take place slowly at temperatures around 100° . When the sample was held for hours at 100° a small but perceptible expansion, which showed no signs of stopping, could be observed. These qualitative observations led to the conclusion that the first break on the heating curve of Form II merely represents the temperature at which the inversion proceeds rapidly enough to be detected thermally and that the temperature above which Form II ceases to be stable is certainly below 100° .

x-Ray Diffraction Experiments. — Powder diffraction

photographs were made with unfiltered Cu K radiation. The samples of

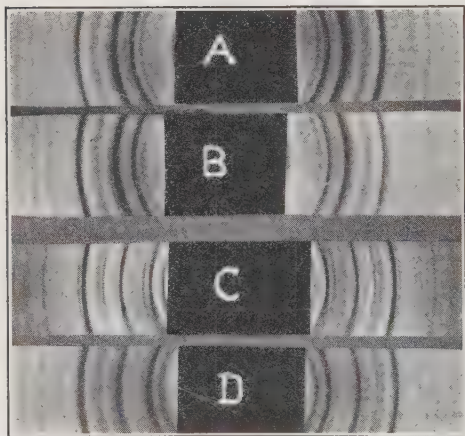


Fig. 4.—x-Ray diffraction patterns of 3-phenyl-2,4-thiazolidione

(10) The difference between the temperatures at which the compound melted in the thermal analysis apparatus (146°) and at which it melted in a capillary tube placed in an electrically heated air-bath ($147\text{--}148^{\circ}$) has been partially accounted for by the fact that the latter apparatus gives results which are too high. In a capillary tube immersed in a stirred oil-bath whose temperature was read by thermocouple A, Form I melted between 146 and 147° , a melting temperature definitely higher than 146° as observed in the thermal analysis apparatus. We are unable at present to give a satisfactory explanation of this slight discrepancy.

3-phenyl-2,4-thiazolidione were mounted on hairs in the centers of cylindrical cameras with a radius of about 3.50 cm. From the various samples of the substituted diketone which were examined two different x-ray diffraction patterns were obtained, as is evident from an examination of those reproduced in Fig. 4. Fig. 4-A shows the diffraction pattern given by a sample which had been recrystallized from water. The pattern in Fig. 4-C was obtained from a sample crystallized from glacial acetic acid, a sample which showed the thermal effect at 139°. Patterns A and C are significantly different and correspond respectively to the polymorphic Forms I and II. A portion of the specimen from which Pattern C was obtained was melted, cooled to 140°, seeded with the form crystallized from water, and examined in the x-ray spectrograph. The result was Fig. 4-B which is identical with Fig. 4-A. A sample known definitely to be Form I was heated until it was completely melted and then plunged into ice water. The x-ray diffraction pattern of the resultant solid, Fig. 4-D, was the same as that of Form II, Fig. 4-C. The experiments establish quite definitely the fact that 3-phenyl-2,4-thiazolidione exists in at least two solid modifications.

It is noteworthy that the two forms have optical properties which are so closely alike that it was impossible to state confidently from results of a casual examination under a polarizing microscope that there was an actual difference in crystal form.

Stability Relations.—The fact that heat is absorbed when Form II transforms to Form I excludes the possibility of monotropy and shows that this change is an enantiotropic one, that is to say, Form II is the stable phase at lower temperatures while Form I is stable at higher temperatures. This was checked by an experiment in which the two forms were enclosed in a tensimeter and it was found that at room temperature Form I had a greater vapor pressure than Form II. As further confirmation, a sample known definitely to be Form I was placed in contact with a saturated solution of the compound in glacial acetic acid and a trace of Form II was added. In another vessel a sample of Form II and a trace of Form I were left in contact with the saturated solution in acetic acid. The mixtures were allowed to stand at room temperature for several months, being agitated at intervals. In each case the resulting solid phase was found by x-ray powder photographs to consist of Form II.

The inversion of Form II to Form I is of a type which is quite common. With rising temperature the change proceeds only very slowly until the temperature is considerably above the equilibrium value at atmospheric pressure, while with falling temperature Form II shows such reluctance to appear that Form I may remain metastable for a long time even at room temperature.

When a compound exists in two or more solid forms, it is of interest to

inquire whether the phenomenon is due to polymorphism, that is to say, whether molecules of the same structure are built up in different crystal arrays; or whether it is a result of tautomerism in which case differences in molecular structure would in general appear in other phases than the solid ones. N. V. Sidgwick¹¹ suggested a convenient method of distinguishing between the two phenomena in cases where the velocity of transformation of tautomers is small. In the case of two solid forms the method consists of determining the following eutectic temperatures: *a*, Form I- Solid Solvent-Solution of I; *b*, Form II- Solid Solvent-Solution of II; and *c*, Form I-Form II-, Solid Solvent-Solution of I and II. If the phenomenon is one of polymorphism the temperature of eutectic *c* will be not less than the temperature of the eutectic of the more soluble (metastable) solid form, the solution and the solid solvent, as both solid forms contribute the same molecular species to the solution. On the other hand, if the solid forms consist of tautomers, each will contribute its own type of molecules to the solution and hence, unless the tautomeric equilibrium in the solution is very rapid, the temperature of the eutectic *c* will be lower than the temperature of eutectics *a* or *b*.

Table I summarizes the results of experiments to determine the invariant temperatures at which the two solid forms of 3-phenyl-2,4-thiazolidione are in equilibrium with solid and liquid benzene. It will be seen that the experiment indicates, either that the case is one of true polymorphism, or that the velocity of the attainment of tautomeric equilibrium in the solution is extremely high.

TABLE I
EUTECTIC TEMPERATURES IN THE SYSTEM, 3-PHENYL-2,4-THIAZOLIDIONE-BENZENE

Phases in system at equilibrium	Equil. temp., °C.
Liquid benzene-solid benzene	5.34
Solution-solid benzene-Form I	4.98
Solution-solid benzene-Form II	5.09
Solution-solid benzene-Form I-Form II	5.00

Summary

The observation that different samples of 3-phenyl-2,4-thiazolidione melt either at 143-144° or 147-148° in a capillary tube is accounted for by the fact that this compound exists in two solid modifications, Form II which is stable at room temperature and Form I which, although stable only at higher temperatures, is capable of existing indefinitely in a metastable state at room temperature. The transformation of Form II to Form I goes so reluctantly that when the compound is heated rapidly, as in a capillary tube, Form II may actually melt metastably before the inversion to the stable phase occurs.

(11) Sidgwick, *J. Chem. Soc.*, **107**, 672 (1915).

OPTICAL CRYSTALLOGRAPHY OF 3-PHENYL-2,4-THIAZOLIDIONE

The faintly yellow crystals of 3-phenyl-2,4-thiazolidione were studied by means of the petrographic microscope and the goniometer. For nomenclature see Part I of this paper.

Form I (higher temperature). Needles with refractive index β parallel to their length; optic axes, showing indistinctly curved bars, without apparent dispersion, and representing $-2V$ about 80° , emerge from the sides of the needles.

$\alpha = 1.570$, $\beta = 1.696$, $\gamma = 1.779$. The preparation examined was crystallized from water.

Form II (lower temperature). Rectangular, monoclinic blades, with refractive index β and crystallographic axis b parallel to their length, flattened parallel to the front pinacoid; cleavage on the base (angle $\beta = 78.5^\circ$) perfect, and on the side pinacoid poor. An optic axis showing a straight bar, without apparent dispersion, is directed within the crystal 3.5° toward axis a from normal to the plane of flattening. $\alpha \wedge c = 41 \pm 2^\circ$ in obtuse angle β . $\alpha = 1.575$, $\beta = 1.693$, $\gamma = 1.805$, from which $-2V =$ about 83° . The preparation was crystallized from glacial acetic acid.

The orientation, the optic axial angle, and the refractive indices α and β are so similar in the two forms that measurements of γ were required to establish the essential optical difference. Even then a knowledge that the fine-grained preparations contained no disturbing contaminant was necessary. One preparation from water contained both needles and blades. Refractive index β of the needles was definitely the higher. The immersion liquids used between 1.74 and 1.79 were saturated solutions of sulfur in mixtures of methylene iodide and iodobenzene.

VITA

Klare Stephen Markley was born December 16, 1895, at Philadelphia, Pennsylvania, the son of Jonah J. and Mabel (Montague) Markley. He received his elementary education in the grade schools of Allentown, Kutztown and Nazareth, Pennsylvania, and Washington, D. C., after which he attended the Rockville (Maryland) Academy, graduating in 1914. He entered The George Washington University in the fall of 1914 but withdrew in 1916 to accept employment. From 1916 to 1921 he was employed as chemist with the Bethlehem Steel Corp., Bethlehem, Pa., the Wharton Steel Company (now defunct), Wharton, N. J., and subsequently as chief chemist of the Valley Mould and Iron Corp., Sharpsville, Pa.

Returning to Washington in 1921 he re-entered The George Washington University from which institution he received the degrees of B.S. in chemical engineering in 1924 and M.S. in chemistry in 1925. He entered The Johns Hopkins University in 1925 and continued in attendance until 1928 when he was granted leave of absence to complete work upon his dissertation at the United States Department of Agriculture. The degree of Doctor of Philosophy with organic chemistry as principal subject was granted in 1929.

In December, 1921, he was married to Calla Inez Lepper of Anoka, Minnesota.

He was employed at the National Bureau of Standards as associate chemist and as assistant and later as associate biochemist with the United States Department of Agriculture. Abstractor for Chemical Abstracts, 1929-30; and collaborator for Biological Abstracts, 1928-30; fellow of the American Association for the Advancement of Science; member of the American Chemical Society, Cosmos Club, Sigma Xi and Alpha Chi Sigma. Author or co-author of twenty papers in organic and phytochemistry.

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